wherein prostaglandin was used alone. However, the Examiner suggests that such properties are considered inherently possessed by the cited art. In response, Applicants respectfully disagree.

As stated in MPEP § 2112 and the Court of Appeals for the Federal Circuit in *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (1993),

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.

Instead, as also stated in MPEP § 2112 and the Court of Appeals for the Federal Circuit in *In re Robertson* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (1999),

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'

As discussed at page 11, lines 9-22, of the instant application, literature concerning reversing priapism with NO synthase inhibitors, as well as studies on analgesia and NO, actually provides one of skill in the art with the expectation of **an increase** in pain upon administration of an agent which increases cAMP, not **a decrease** in pain as is presently claimed. Accordingly, extrinsic evidence in this art actually teaches away from the missing descriptive matter, namely pain management, being a feature of the treatment regime of the '803 patent. Clearly, a person of ordinary skill in the art would not recognize **pain management** as a feature being present in the therapy taught by the '803 patent.

Thus, inherency has not been established because the two prong test set forth in *In re Robertson, supra,* has not been met. First, the '803 patent does not make clear that pain management is present in the therapy taught therein, and second, based upon the extrinsic evidence, a skilled artisan would not even recognize pain management to be present.

However, there is more. The '803 patent discloses that the nitroglycerin dose used to treat erectile dysfunction is very high compared to the dose of nitroglycerin normally given to angina pectoris patients (see col. 3, lines 22-24). In particular, the '803 patent teaches a dose range of 0.5 to 5 mg, preferably, 0.5 to 2.5 mg of nitroglycerin alone or in combination with another agent to treat impotence (please see, col. 3, lines 20-22 and Table 1 at col. 4, 5 and 6).

In contrast, the instant disclosure and claims set forth the use of a low dose of a NO producing agent. The Examiner's attention is respectfully directed to page 8, lines 8-12, wherein it is taught that a low dose of for example, 50 μg of SNP, which does not product significant systemic side effects is combined with a low to moderate dose of PGE1. This low dose of SNP was also administered to patients in Case Nos. 4, 5 and 6 (described at pages 17 and 18 of the specification) and demonstrated to be effective at decreasing the pain associated with administration of the prostaglandin required to produce the erection. For nitroglycerin, Case Nos. 2 and 3 at page 17 of the specification describe application of a Nitropatch delivering nitroglycerin at a rate of 0.2 mg/hour 10 to 20 minutes prior to injection of a PGE1. This dose of nitroglycerin is 7.5- to 15-fold lower than the lowest dose taught or disclosed to be useful by the '803 patent.

Accordingly, in an earnest effort to advance the prosecution of this case and to highlight distinctions between the instant invention and the teachings of the cited art, Applicants have amended the claims to recite that the NO producing agent or the agent that augments action of cGMP is administered at a low dose which does not produce significant systemic side effects. Support for this amendment can be found in the specification at for example, page 8 and pages 17-18 as discussed *supra*.

The '803 patent provides no teaching whatsoever of administration of nitroglycerin or any other NO producing agent at low doses. Thus, this reference cannot anticipate the claims as amended.

As such, withdrawal of this rejection under 35 U.S.C. § 102(e) is respectfully requested in light of the above arguments and the amendments to the claims.

IV. Rejection of Claims 60-80 under 35 U.S.C. § 103(a)

Claims 60-80 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,894,803 in view of Akkus *et al.* (Medline Abstract, AN 95174112) and Cesar *et al.* (WO 94/04120). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

In accordance with MPEP § 2143, to render an invention *prima facie* obvious, the combination of prior art must meet three basic criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, the combination of prior art references must provide a reasonable expectation of success. Third, the combination of prior art must teach or suggest all the limitations of the claims. The combination of cited art references in the instant rejection fails to meet these criteria.

As discussed in Section III, *supra*, the pending claims have been amended to clarify that in the pain decreasing method of the present invention, the NO producing agent or the agent that augments cGMP is administered at a low dose which does not produce significant systemic side effects. As the Examiner is aware, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

The teachings of the '803 patent make clear that side effects exist for most known erectile dysfunction medication, such as risk of infection, bruises, fibrosis and scarring with permanent changes inside the penis. There is also a risk of a painful longstanding erection (priapism). As disclosed in the '803 patent at the bottom of Table I (column 5), in the 33 patients given the patented treatment, side effects were seen in 12 patients.

There is simply no teaching or suggestion to modify the teachings of the '803 patent to arrive at the instantly claimed invention. The '803 patent provides a treatment that has similar side effects as other known treatments for erectile dysfunction. The '803 patent teaches a dose range of 0.5 to 5 mg, preferably 0.5 to 2.5 mg of nitroglycerin alone or in combination with another agent to treat impotence. There is absolutely no teaching or suggestion of reducing side effects, or reducing the pain of prostaglandin treatment, by using a low dose of a NO producing agent as is currently claimed.

Further, as acknowledged by the Examiner, the '803 patent does not teach or suggest the use of nitroglycerin in combination with prostaglandin to manage pain associated with prostaglandin administration for erectile dysfunction. Accordingly, this reference also provides no reasonable expectation of success that administration of a low dose of nitroglycerin or another NO producing agent would be effective at decreasing pain associated with use of prostaglandins for treatment of erectile dysfunction.

As discussed in Section III, *supra*, the '803 patent provides no teaching or suggestion of administration of low doses of nitroglycerin or other NO producing agents. Accordingly, this reference fails to teach or suggest all the limitations of the claims as amended.

Applicants assert that the secondary references fail to remedy the deficiencies of the primary reference cited in this rejection.

The Abstract by Akkus *et al.* is merely a report of an "unusual case" of clitorimegaly wherein intracorporeal injection of prostaglandin E1 resulted in marked clitoral erection. There is no discussion whatsoever of administration of a NO producing agent or an agent that augments cGMP, nor doses at which they would be administered.

WO 94/04120 teaches the use of histamine H2 receptor agonists and/or histamine H3 receptor agonists for treatment of erectile dysfunction in animals, particularly humans. Use of NO producing agents to treat male impotence is discussed in the Background Section of this PCT application. The NO producing agent, SIN, is disclosed as being considerably less effective than PGE1 and is taught not to play a role

in the management of male impotence. There is no other disclosure of NO producing agents in this reference.

Accordingly, this combination of references provides no reasonable expectation of success that administration of a NO producing agent or an agent that augments cGMP would be useful in decreasing the pain associated with prostaglandin administration for erectile dysfunction.

Further, the combination of cited art provides no teaching or suggestion whatsoever of the limitation in the amended claims of administering a NO producing agent or an agent that augments cGMP at a low dose which does not produce significant systemic side effects. Thus, the cited combination of art fails to meet the criteria required to render the instant claimed invention obvious.

In view of the foregoing, a *prima facie* case of obviousness has not been established. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

V. Supplemental IDS

Applicants are submitting herewith for the Examiner's consideration a Supplemental Information Disclosure with attached references and the requisite fee for filing an IDS after the period set forth in §1.97(b) but before the mailing date of either a Final Rejection or Notice of Allowance.